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(54) UTILISATION DE ROTIGOTINE EN TRAITEMENT DE DEPRESSIONS

(54) USE OF ROTIGOTINE FOR THE TREATMENT OF DEPRESSION

(57)

The invention relates to the use of rotigotine [(-)  
-5,6,7,8-tetrahydro-6- [propyl[2-(2-thienyl)  
ethyl]amino]-1-naphthol] and the prodrugs and  
pharmaceutically acceptable salts thereof for the  
production of a medicament used to treat depression.



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(54) Titre : UTILISATION DE ROTIGOTINE EN TRAITEMENT DE DEPRESSIONS  
(54) Title: USE OF ROTIGOTINE FOR THE TREATMENT OF DEPRESSION

(57) Abrégé/Abstract:

The invention relates to the use of rotigotine [(*-*)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol] and the prodrugs and pharmaceutically acceptable salts thereof for the production of a medicament used to treat depression.

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## **Abstract**

The present invention relates to the use of rotigotine [(-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol] and its prodrugs and pharmaceutically acceptable salts for producing a pharmaceutical agent for treating depression.

## Use of rotigotine for the treatment of depression

### Description

According to estimates of the WHO, depression will be the second most common cause of disability caused by illness by 2020 (Murray, Lancet 349 (1997) 1498). The efficiency of current pharmacological treatments is limited for various reasons, for example because of late onset of effect, side effects or lack of effectiveness of the pharmaceutical agents. There is a great need for new, innovative antidepressants because of the frequency and duration of this illness and the tendency to relapse.

Until now, amine reuptake inhibitors or monoamine oxidase inhibitors have primarily been used as antidepressants (Goodman & Gilman's, The pharmacological basis of therapeutics, 9th Edition). Very recently, the use of active ingredients, which influence both serotonergic (5HT<sub>1</sub>) and adrenergic receptors ( $\alpha_2$ ) has been discussed as a very promising therapy concept (Westenberg, J. Clin. Psychiatry 60, Suppl. 17, 1999, 4; Schatzberg, Human Psychopharmacology 17, 2002, p. 17). One example of an active ingredient with a dual action principle of this type is mirtazapine (Gorman, J. Clin. Psychiatry 60, Suppl. 17, 1999, 9).

A fast onset of action and superior effectiveness in comparison to conventional antidepressants is expected from active ingredients with a dual action principle, as the high selectivity of the active ingredients and the favourable side effect profile connected therewith allows a rapid adjustment of the patient to the individual maintenance dose (Deakin, Int. Clin. Psychopharmacology 17, Suppl. 1, 2002, p. 13).

The dopamine agonists pramipexol and ropinirol were recently attributed an antidepressive effectiveness and this effect was demonstrated in clinical studies (Ostow, M., Am J Psychiatry. 2002 Feb; 159(2):320-1). However, it is still unclear here as to what contribution the dopamine agonism and what contribution possible other effects of the dopamine agonists investigated make as these also influence other neurotransmitter systems substance-specifically.

It has now surprisingly been found that the rotigotine described as a dopamine agonist (Metman, Clinical Neuropharmacol. 24, 2001, 163) binds both to  $\alpha_2$  receptors and to the 5HT1A receptor. While rotigotine acts antagonistically on  $\alpha_2$  receptors, it exhibits agonistic activity on 5HT1A receptors.

With this profile, in particular with respect to the surprising agonistic 5HT1A activity, rotigotine [(-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol] is a candidate for use as an antidepressant.

The suitability of rotigotine as an antidepressant was demonstrated in three different, validated animal models.

The "forced swim test" is an animal model, in which depressive episodes are triggered by acute stress. In this case, rats are forced to swim in a limited space. After initial attempts to save themselves, in which the animals grasp the hopelessness, they lapse into immobility. On repetition of the experiment, the animals remain immobile from the beginning of the experiment. In the event of pre-treatment with antidepressants, the period of immobility is shortened during the repetition experiment; the animals generally start searching and escape movements directly after transfer into the water basin (Porsolt, Biomedicine 30, 1979, 139). Rotigotine leads to a significantly shortened period of immobility.

In the "learned helplessness test", rats are repeatedly subjected to uncontrollable stress. This brings about an impaired learning ability in the animals in a later situation (for example after 48 h), in which they could escape the stress again. After sub-chronic, but not acute administration of antidepressants, the learning ability normalises again and the animals learn to escape the (announced) stress (in time), (Sherman, Pharmacology Biochemistry & Behavior 16, 1982, 449). After several days of administration of rotigotine depot suspension (Embodiment 2) the animals exhibited improved learning behaviour at low concentrations; nevertheless the higher doses also increased the activity of the animals under non-test conditions.

In a further animal model (Embodiment 3) an investigation was made as to whether the antidepressive effects of rotigotine can be distinguished from a general motor

stimulation. In this case, rotigotine was administered to rats, whose olfactory bulb had been removed on both sides. The removal of the olfactory bulb leads in the untreated control group to an adaptive hyperactivity. It is known from the literature that chronically administered antidepressants lead to a reduction in movement activity of the animals in this model, while stimulants further increase the motor activity (van Riezen H et al, Br J Pharmacol. 60(4), 1977, 521; Kelly JP et al, Pharmacol Ther. 74(3), 1997, 299). Therefore, it is possible to discriminate between antidepressive and non-specific stimulatory effects of an active ingredient with this model. It has been shown that rotigotine exhibits a specifically antidepressive effect in low doses that approximately corresponds to the effect of the antidepressant imipramine and which leads to virtually complete suppression of the bulbectomy-induced locomotor hyperactivity. In higher rotigotine concentrations, on the other hand, the stimulatory dopamine-agonistic effect predominates.

It could thus be clearly shown that subcutaneously applied rotigotine surprisingly has a significant antidepressive effect in all three tests.

Fig. 1 shows that rotigotine leads to a clear reduction in the immobility period in the "forced swim test".

Fig. 2 shows that animals treated with rotigotine depot suspension (Embodiment 2) in the "learned helplessness test" exhibit a normalised learning behaviour (NHC), depending on the dose, compared to the control group (HC) treated only with excipient.

Fig. 3 shows that rotigotine in low doses in bulbectomised rats (Embodiment 3) significantly reduces the motor hyperactivity and therefore develops a clear antidepressive effect. In higher doses, on the other hand, a non-specific activation of the locomotor activity dominates and occurs both in bulbectomised animals and also in control animals.

The conclusion emerges from these preclinical data that new effective pharmaceutical agents can be made available for treating depression with rotigotine, its biologically active metabolites and the corresponding prodrugs and salts.

A subject of the invention is therefore the use of rotigotine, its prodrugs and salts for producing a pharmaceutical agent for treating depression. The term "treating" in this patent application comprises both the treatment of existing depression and the preventative treatment (prophylaxis) of depression, for example of recurring depressive phases.

Depressive disorders are divided for better understanding and to achieve an optimum individual therapy into subforms, with the transitions of the various subforms often being blurred. Depression is classified - traditionally - according to its presumed causes or - latterly - according to its symptoms (see in this regard ICD-10 "International Statistical Classification of Diseases and Related Health Problems" of the WHO).

In this application, the term "depression" is taken to mean both the various traditional subforms of depression mentioned below and the disorders subsumed under the term "affective disorders" in ICD-10, which accompany depressive episodes, in particular depressive episodes, recurrent depressive disorders, depressive phases in bipolar affective disorders and anxiety disorders, adaptation disorders and organic brain diseases which accompany depressive symptoms in each case. Corresponding disorders are listed, for example in the ICD-10 classifications (Version 2.0, November 2000) F31, F32, F33, F41, F43, F45 and F06.

In the conventional division of depression according to causes, 4 main classes are generally distinguished:

#### I. Endogenous depression

No easily discernible external causes can be identified as triggers of the depression in endogenous depression. Triggers are probably disorders of the neurotransmitter system of the brain. The phase-like course where the depressive episodes can occur repeatedly is typical of endogenous depression. Endogenous depression is generally divided into

- unipolar depression ("major depression"), in which only depressive phases occur
- bipolar depression ("manic-depressive disorders"), in which depressive episodes alternate with manic phases.

## II. Somatogenic depression

Physical-organic disorders are the cause of this depression. Generally, somatogenic depression is divided into

- organic depression, based on an illness or injury to the brain. Such illnesses or injuries, which are often accompanied by a changed brain metabolism are, for example, brain tumours, Parkinson's disease, migraines, epilepsy, brain paralysis, arteriosclerosis of the brain, brain traumas, meningitis, stroke and dementias, such as, for example, Alzheimer's disease;
- symptomatic depression which often occurs as a result of or as an accompanying symptom of an illness which only indirectly influences the brain function. This may be, for example a circulatory illness, hypothyroidism, or another hormone disorder, infectious disease, cancer or liver disease;
- pharmacogenic depression, for example in the case of alcohol, medication or drug misuse.

## III. Psychogenic depression

This is often an overreaction to one or more traumatic experiences. It is frequently subdivided into exhaustion-depression, neurotic depression and reactive depression on the basis of current conflicts or events.

## IV. Depression in particular circumstances

Examples are postpartum depression, age depression, childhood depression, seasonal depression and puberty depression.

Rotigotine and its prodrugs and salts are basically suitable for the production of a medication for treating the various, above-mentioned forms of depression or for

treating affective disorders, in particular depressive episodes, recurring depressive disorders and depressive phases in bipolar affective disorders, according to ICD-10.

According to the invention, rotigotine is preferably used for producing a medication for treating depressive episodes and serious recurring depressive disorders such as occur, for example in endogenous, unipolar depression ("major depression").

Metabolic disorders of the brain cells, i.e. noradrenaline or lack of serotonin and/or a genetic predisposition are regarded as causes of endogenous, unipolar depression.

Designated under the term "major depression" in this application is, in particular, a disorder such as described in the American diagnosis manual "The Diagnostic and Statistic Manual of Mental Disorders - 4th Edition" (American Psychiatric Association, 1994; "DSM IV").

Rotigotine  $\{(-)-5,6,7,8\text{-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol}\}$  and its prodrugs and salts are also especially suitable for producing antidepressants for treating depressive episodes in manic-depressive patients. These depressive phases in bipolar disorders are subsumed in this patent application under the term "depression".

Rotigotine is also preferably used for producing a pharmaceutical agent for treating "organic" depression, as described above. Organic depression occurs frequently, for example, in Parkinson's diseases, or in cerebrovascular diseases and in dementia disorders.

In the treatment of depression, which occurs as a result of Parkinson's disease, the conclusion which is relevant for clinical practice emerges from the present invention that the conventional comedication of antidepressants and anti-Parkinson's agents is not required when the depressive Parkinson's patients are put on rotigotine.

A subject of the invention is therefore the use of rotigotine, its metabolites, prodrugs and salts, for producing a pharmaceutical agent for the treatment of depression

associated with Parkinson's disease, it being possible optionally to dispense with a comedication with other antidepressants.

Another subject of the invention is the use of rotigotine, its metabolites, prodrugs and salts, in each case alone or in combination with other antidepressants, for treating organic depression, which is not associated with Parkinson's disease. Examples of such organic depression is depression in conjunction with brain tumours, migraines, epilepsy, brain paralysis, brain arteriosclerosis, brain traumas, meningitis, stroke, dementia, Alzheimer's disease or the Parkinson Plus Syndrome.

A further subject of the invention is a method for treating depression in a mammal, in particular endogenous, unipolar depression ("major depression"), a depressive phase of a bipolar disorder, Parkinson's-associated depression or an organic depression which is independent of Parkinson's disease by administering a therapeutically effective quantity of rotigotine, a metabolite, prodrugs or salt to said mammal, in particular to a human.

"Prodrugs" of rotigotine are taken in this patent application to mean, in particular compounds which are cleaved, converted or metabolised in the human body, in particular in the plasma or when passing through skin or mucous membrane in an effective quantity to form rotigotine.

Example of prodrugs are esters, in particular alkanoyl esters and particularly preferably alkanoyl esters with up to 6 carbon atoms. Other examples of prodrugs are carbamates, carbonates, ketals, acetals, phosphates, phosphonates, sulphates and sulphonates.

The production of prodrugs by the reaction of rotigotine with correspondingly reactive precursors such as acid chlorides, acid anhydrides, carbamoyl chlorides, sulphonyl chlorides etc. is known to the person skilled in the art in the area of medical chemistry and can be found in the relevant technical literature.

Examples of literature references are Bundgaard: Design of Prodrugs, Elsevier, Amsterdam, 1985; Higuchi and Stella: Pro-drugs as novel drug delivery systems in

American Chemical Society, Washington DC, 1975; Sloan: Prodrugs - Topical and Ocular Drug Delivery, Ed: M. Dekker, 1992; Roche: Design of biopharmaceutical properties through prodrugs and analogs, Washington, DC, 1977.

The basic suitability of a rotigotine derivative as a prodrug can be determined in that the respective compound is incubated under defined conditions with an enzyme mixture, a cell preparation, a cell homogenate or an enzyme-containing cell fraction and the rotigotine developing is measured. A suitable enzyme mixture is, for example, contained in the S9-liver preparation from Gentest, Woburn, MA, USA. To measure prodrugs which can be cleaved especially rapidly, the prodrug to be tested can also be incubated in plasma, for example plasma from human blood. The optimum hydrolysis speed of the prodrug depends on the objective. Prodrugs which can be cleaved rapidly may be suitable, for example for rapid flooding, for example in the case of nasal administration. Prodrugs which can be cleaved more slowly may be suitable, for example for retardation, for example in the case of transdermal, parenteral or oral administration.

Various prodrugs of the racemate of rotigotine (N-0437) are described, for example, in Den Haas et al., Naunyn-Schmiedeberg's Arch Pharmacol 342, 1990, 655 and Den Haas et al, J. Pharm Pharmacol 43, 1991, 11.

In vivo, a prodrug should release so much rotigotine that a therapeutically effective steady-state concentration of rotigotine is obtained in the plasma. Generally regarded as therapeutically effective concentrations here are rotigotine concentrations between 0.05 and 20 ng/ml, preferably between 0.1 and 10 ng/ml and particularly preferably between 0.2 and 5 ng/ml plasma.

For the specific treatment of depression, however, lower rotigotine plasma levels may optionally be adequate, for example those under 2 ng/ml, for example between 0.05 and 1 ng/ml plasma or between 0.1 and 0.5 ng/ml plasma.

Rotigotine is the S-(-)-enantiomer of 5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol. This means that the proportion of (R)-enantiomers in the pharmaceutical agent is small according to the invention. The (R)-enantiomer is

preferably present in a proportion of < 10 mol%, particularly preferably in a proportion of < 2 mol% and quite particularly preferably at a mol proportion of < 1%, based on the total quantity of rotigotine in the antidepressant.

Rotigotine and its prodrugs can be present in the pharmaceutical agent as free bases or in the form of physiologically acceptable salts, for example in the form of hydrochloride.

"Physiologically acceptable salts" include non-toxic addition salts of a base, in particular a compound of a formula (I) in the form of the free base, with organic or inorganic acids, for example with HCl.

There are many methods of application for administering rotigotine and its prodrugs which the person skilled in the art can select and adapt depending on the need, state and age of the patient, required dosage and desired application interval.

A preferred type of administration of rotigotine is transdermal administration. The administration form may in principle be selected from, for example an ointment, paste, spray, film, plaster or an iontophoretic device.

Rotigotine is preferably applied, in this case, in plaster form to the skin of the patient, the active ingredient preferably being present in a matrix made of adhesive polymer, for example a self-adhesive adhesive polysiloxane (Embodiment 1). Examples of suitable transdermal formulations are to be found in WO 99/49852, WO 02/89777 and WO 02/89778. A form of administration of this type allows a substantially constant plasma level to be adjusted and therefore a constant dopaminergic stimulation over the entire application interval (WO 02/89778; Metman, Clinical Neuropharmacol. 24, 2001, 163).

If, on the other hand, an antidepressant in the form of a subcutaneous or intramuscular depot form is desired, the rotigotine may be suspended, for example as a salt crystal, for example as a crystalline hydrochloride in a hydrophobic anhydrous medium and injected, as described in WO 02/15903 or else administered in the form

of microcapsules, microparticles or implants based on biodegradable polymers, such as described in WO 02/38646, for example.

Other conceivable forms of administration of rotigotine and its prodrugs are transmucosal formulations, for example sublingual sprays, nasal or rectal formulations or aerosols for pulmonary administration.

Suitable dosages of rotigotine are between 0.1 and about 50 mg/day, with daily doses preferably between 0.2 and 40 mg and in particular between 0.4 and 20 mg/day being administered. Particularly preferred dosages of rotigotine are above 0.5 mg/day, wherein for rotigotine applications, which do not require simultaneous treatment of Parkinson's disease motor disorders, such dosage forms are quite particularly selected in which the antidepressive effect of rotigotine is marked, but in which the non-specific stimulatory effect of rotigotine is as small as possible. Such dosages are, in general below 10 mg/day, for example below 7.5 mg or below 5, 4, 3, 2 or below 1 mg/day and in particular between 0.5 and 5 mg/day.

In the case of Parkinson's disease, on the other hand, a dosage of sometimes above 5 mg/day may be required for simultaneous therapy of the motor disorders. Corresponding dosages are, for example dependent on the age and condition of the patient, degree of severity of the illness etc., sometimes significantly above 1 mg/day, for example over 5, 6, 8, 9, 10 or even between 10 and 50 mg/day, for example between 10 and 25 mg/day.

Depending on the selected type of application, the desired daily dose may be controlled by the formulation design. For example, the daily dose of transdermally administered rotigotine can be adjusted by means of the adjustment of a corresponding flux rate per unit of area and/or by variation of the plaster size. In this case, the dosage may take place in a creeping fashion, in other words the treatment may optionally start with low dosages which are then increased to the maintenance dose.

A subject of the invention is therefore a dosage form, for example a plaster or an injectable deposit formulation which releases the appropriate required quantity of

rotigotine for therapy of the depression, for example between 0.5 and 10 mg/day or between 0.5 and 5 mg/day, as described above.

It is clear to the person skilled in the art that the dosage interval may vary depending on the applied quantity, the type of application and the daily requirement of the patient. Thus a transdermal application form may be conceived, for example for a once daily, once every three days or once every seven days administration, while a subcutaneous or intramuscular depot may make possible injections, for example in a one-week, two-week or four-week rhythm.

Rotigotine and its prodrugs can be used as monotherapeutic agents for treating depression. In one embodiment of the invention, however, other active ingredients may be present, apart from rotigotine, in the antidepressive therapeutic agent form.

Examples of this are other antidepressants which directly or indirectly influence the serotonin or noradrenaline metabolism.

Examples of this are

- selective serotonin reuptake inhibitors, such as sertraline, citalopram, paroxetine or fluoxetine
- mixed serotonin and noradrenaline reuptake inhibitors such as venlafaxine, milnacipram, mirtazapine and tricyclic antidepressants such as amitriptyline and imipramine
- selective noradrenaline reuptake inhibitors such as reboxetine
- monoamine oxidase inhibitors such as tranylcypamine or clorgyline
- Alpha2-receptors and/or serotonin receptor-modulators such as mirtazapine or nefazodone.

Other examples of antidepressants are adenosine antagonists, such as for example, ST 1535, Sigma-opioid receptor ligands, NK antagonists such as GW 597599, saredutant or aprepitant, melatonin agonists or modulators of the hypothalamus-hypophysis-adrenal axis.

Depending on the cause and the symptoms of the depression, a combination preparation may also contain an additional antipsychotic, sedative, anxiolytic or migraine agent, or an active ingredient which develops one or more effects selected from an antidepressive, antipsychotic, sedative, anxiolytic or anti-migraine effect.

In the process the compound of Formula I or II and the additional antidepressant, antipsychotic, sedative, anxiolytic or migraine agent may be present in the same pharmaceutical formulation, for example a combination tablet, or else in different application units, for example in the form of two separate tablets. Depending on need, the two active ingredients may be administered simultaneously or temporally separately.

In a combination preparation, a sequential administration can be achieved, for example, in that an administration form, for example an oral tablet, has two different layers with a different release profile for the various pharmaceutically active ingredients. It is clear to the person skilled in the art that, in the context of the present invention, various forms of administration and application patterns are conceivable, which are all the subject of the invention.

Examples of antipsychotics are promethazine, fluphenazine, perphenazine, levomepromazine, thioridazine, perazine, promazine, chlorprothixene, zuclopenthixol, prothipendyl, flupentixol, zotepine, benperidol, pipamperon, melperon, haloperidol, bromperidol, sulpiride, clozapine, pimozide, risperidone, quetiapine, amisulpride, olanzapine.

Examples of sedatives are diphenhydramine, doxylamine succinate, nitrazepam, midazolam, lormetazepam, flunitrazepam, flurazepam, oxazepam, bromazepam, triazolam, brotizolam, temazepam, chloral hydrate, zopiclone, zolpidem, tryptophan, zaleplon.

Examples of anxiolytics are fluspirilene, thioridazine, oxazepam, alprazolam, bromazepam, lorazepam, prazepam, diazepam, clobazam, medazepam, chlordiazepoxide, dipotassium chlorazepate, nordazepam, meprobamate, buspirone, kavain, hydroxyzine.

Examples of migraine agents are almotriptan, zolmitriptan, acetylsalicylic acid, ergotamine, dihydroergotamine, methysergide, ipرازochrome, ibuprofen, sumatriptan, rizatriptan, naratriptan, paracetamol.

#### Embodiments:

##### Embodiment 1: Rotigotine plaster

1.8 g rotigotine (free base) are dissolved in 2.4 g ethanol and added to 0.4 g collidone 90F (dissolved in 1 g ethanol). This mixture is added to a 74% solution of silicone polymers (8.9 g BioPSA 7-4201 + 8.9 g BIO-PSA 7-4301 [Dow Corning]) in heptane. After the addition of 2.65 g petrol ether, the mixture is stirred for 1 hour at 700 rpm in order to obtain a homogeneous dispersion. After lamination on polyester it is dried at 50°C. The plaster weight was finally 50 g/cm<sup>2</sup>.

##### Embodiment 2: Rotigotine depot suspensions

(a) 1411.2 g Miglyol 812 was weighed into a Duran flask. 14.4 g Imwitor 312 were added to the Miglyol and then heated for 30 minutes to 80°C whilst stirring. The clear solution was cooled to room temperature and filtered.

(b) 1188 g of the solution produced under (a) were transferred into a glass laboratory reactor, 12 g rotigotine were added and homogenised for 10 minutes under nitrogen with an Ultraturrax at 10,000 rpm. The suspension was decanted into brown glass bottles with the Ultraturrax running (2,000 rpm).

##### Embodiment 3:

The bulbectomy study was carried out on Sprague-Dawley rats. A group, which had seemingly been operated on, served as a control group and was operated on without the olfactory bulb being removed. 14 days after the operation, the rats were treated with excipients, rotigotine depot suspension (every second day) or imipramine. On

test days, the rats were taken onto a test field and left to themselves for 3 minutes. The locomotor activities of the animals were measured here with the aid of the number of lines crossed.

## Claims

1. Use of rotigotine [(*-*)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol] and its prodrugs and physiologically acceptable salts for producing a pharmaceutical agent for treating depression.
2. Use according to claim 1, wherein the depression is a unipolar depression [major depression] or a depressive episode of a manic-depressive disorder.
3. Use according to claim 1, wherein the depression is an organic depression.
4. Use according to claim 3, wherein the depression is an organic depression which is independent of Parkinson's disease.
5. Use according to claim 3, wherein the depression is a Parkinson's disease-associated depression.
6. Use according to any one of the preceding claims, wherein the pharmaceutical agent is provided for parenteral, transdermal or mucosal administration.
7. Use according to any one of the preceding claims, wherein the rotigotine is administered in a dosage of 0.5 to 50 mg per day.
8. Use according to any one of the preceding claims, wherein the prodrug is an ester, carbamate, carbonate, ketal, acetate, phosphate, phosphonate, sulphate or sulphonate.
9. Combination preparation for treating depression, comprising rotigotine and a further active ingredient from the group of antidepressants, antipsychotics, sedatives, anxiolytics or migraine agents.

10. Method for treating depression in a mammal, comprising the administration of a therapeutically effective quantity of rotigotine or a rotigotine prodrug or salt to said mammal.

Application number / numéro de demande: EPO4/08168

Figures: 1-2-3  
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